Leptin in Energy Balance and Reward: Two Faces of the Same Coin?

Leptin receptors are expressed on mesolimbic dopamine neurons, yet little is known about the functional significance of this anatomical relationship. In this issue of *Neuron*, Hommel et al. reveal a novel site for leptin's regulation of feeding. In turn, Fulton et al. propose a novel role for leptin in regulating non-feeding-related motivated behaviors.

Feeding is both a requisite to survival as well as a gratification for the palate. It is, in fact, common experience to eat beyond need, solely because the food served on our plates is particularly delicious. In westernized societies, the ready availability of food and a thrifty genotype, better adapted to deal with conditions of scarcity, work against us and lead to the development of obesity. However, the increasing worldwide prevalence of obesity and its sequelae, such as diabetes and cancer, represents a serious health threat. Thus, understanding the many factors that affect eating behavior is of substantial interest to the scientific and medical community.

The central nervous system (CNS) processes the smells, tastes, and images of food. It also integrates information about different aspects of eating behavior with hormonal signals related to hunger, satiety, and levels of stored energy in the form of adipose tissue. Energy balance is maintained through regulation of body fat, in part via feedback signals arising from fat depots that are sensed by the brain. The hormone leptin, synthesized in adipose tissue, circulates in proportion to body fat and informs the CNS about the status of adipose stores (Seeley and Woods, 2003). The classic view of leptin is that it has coordinated actions on the activity of a number of hypothalamic systems that in turn are responsible for regulating ingestive behavior (Seeley and Woods, 2003).

Despite the clear role of such homeostatic factors, feeding behavior is greatly influenced by the rewarding properties of the food, independent of its caloric value. A wide range of evidence points to potential parallels between overeating and recognized addictive behaviors, such as abuse of alcohol, nicotine, cocaine, and heroin. Indeed, brain circuits that drive addiction can be deranged by natural rewards like food as happens with drugs of abuse (Volkow and Wise, 2005). For instance, highly palatable food enhances mood in humans (Davis et al., 2004) and, when consumed in excess and over time, produces the same brain neuroadaptations caused by drug abuse (Volkow and Wise, 2005). Moreover, both feeding and drug use are characterized by learned habits and preferences that are acquired and stamped by powerful rewarding reinforcement (Volkow and Wise, 2005).

As the hypothalamus has been identified as a central substrate for the homeostatic regulation of energy balance (Seeley and Woods, 2003), the rewarding properties of food are processed by corticolimbic circuits that link the prefrontal cortex, the amygdala, the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the ventral pallidum with the medial forebrain bundle. Such a network, via neuronal fibers connecting the hindbrain and midbrain to key hypothalamic nuclei, modulates hunger and satiety (Saper et al., 2002; Figure 1).

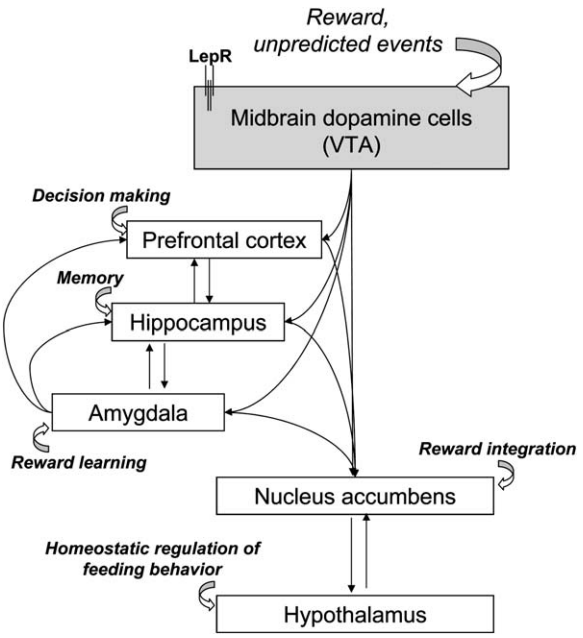

Figure 1. Schematic Model of Brain Circuitry Involved in Motivation and Feeding Behavior

VTA, ventral tegmental area; lepR, leptin receptors. For a more in-depth description of the mesolimbic dopaminergic pathway in reward and food intake regulation, the reader should refer to Saper et al. (2002), Kelley (2004), and Volkow and Wise (2005).

Mesolimbic dopaminergic neurons, arising in the VTA and projecting to the NAc, have long been thought to play a central role in mediating the reinforcing or rewarding properties of drugs of abuse as well as food (Saper et al., 2002). An intact dopaminergic circuit is indispensable for feeding, as dopamine-deficient mice die of starvation (Szczypka et al., 1999). Additionally, when *ob/ob* mice are made unable to synthesize dopamine, they become aphagic. Thus, dopamine is essential to the CNS leptin actions controlling food intake (Szczypka et al., 2000).

Imaging studies in humans have provided evidence of dopamine involvement in the motivational properties of food intake as well as the neurobiological processes driving emotional eating (Volkow and Wise, 2005). Depending on the perceived reward value of the food stimulus, cortical and limbic areas of the human brain are activated, and an increase in extracellular dopamine in the NAc is observed (Volkow and Wise, 2005). Moreover, similarly to what has been reported in drug-addicted subjects, striatal dopamine D2 receptor availability is significantly lower (implying lower sensitivity to reward) in obese subjects, and subjects with the lowest D2 values have the highest BMIs (Wang et al., 2001).

Relatively little is known about the interaction between corticolimbic circuits and the hypothalamus regarding the integrated regulation of feeding behavior.

Studies performed by Kelley and colleagues have clarified that the accumbens shell, but not the core, is a critical link for the overall regulation of food intake, connecting cortical circuits and hypothalamic/brainstem circuits (Kelley, 2004). The NAc can disinhibit neurons in the lateral hypothalamus (LHA) by inhibiting GABAergic striatopallidal projections to the LHA, thus eliciting food intake (Saper et al., 2002). Conversely, feeding responses induced by stimulating the LHA can be prevented by blockade of striatal dopamine (Saper et al., 2002). Moreover, leptin, in addition to reducing food intake, decreases the reward value of brain self-stimulation in the LHA (Fulton et al., 2000). Leptin also has been shown to alter the reward threshold for food (Figlewicz, 2003). Hence, postprandial elevations in leptin may have coordinated effects on both homeostatic and reward circuits to direct ingestive behavior (Figlewicz, 2003).

In this issue of *Neuron*, Hommel et al. (2006) and Fulton et al. (2006) investigate the functional significance of leptin action in VTA dopamine neurons not only to regulate food intake but also to modulate actions of drugs of abuse. Together, these papers importantly expand our understanding of the multiple actions of leptin in the CNS.

In 2003, Figlewicz and colleagues reported that leptin receptors are expressed on VTA dopamine neurons (Figlewicz et al., 2003). These anatomical data, combined with physiological evidence that modulation of the mesolimbic dopamine pathway affects food intake (Saper et al., 2002), provided a logical basis for Hommel et al. (2006) to investigate the role of VTA dopamine neurons in leptin's ability to reduce food intake. Consistent with Figlewicz et al.'s immunohistochemical data (Figlewicz et al., 2003), they observed colocalization of mRNA for leptin receptor and tyrosine hydroxylase (TH), a marker for VTA dopamine neurons, using dual-label fluorescence in situ hybridization. Moreover, when they administered leptin peripherally or directly into the VTA, they observed increased STAT3 phosphorylation in TH-positive neurons. Finally, in vivo and ex vivo electrophysiological recordings revealed that acute leptin treatment reduced the firing rate of VTA dopamine neurons. Consistent with previous work (Figlewicz, 2003), these findings point to a direct inhibitory effect of leptin on VTA dopamine neurons.

To assess whether such VTA regulation is an important component of leptin's ability to regulate food intake, Hommel et al. (2006) administered leptin directly into the VTA and found that leptin decreased food intake over 24 hr. This effect was not secondary to changes in general activity, as leptin had no effect on levels of locomotor behavior. To evaluate the effects of reduced leptin signaling in the VTA, Hommel et al. (2006) used viral-mediated knockdown to selectively ablate leptin receptors in the VTA ($LEPR^{VTA}$). They found that, in the 30 days following viral delivery, $LEPR^{VTA}$ animals displayed increased food intake but did not gain weight, presumably because they also had an increase in locomotor activity. Furthermore, $LEPR^{VTA}$ animals displayed increased consumption of a 0.2% sucrose solution as well as hyperphagia over the first 3 days of consumption of a high-fat diet. Collectively, these data suggest that leptin action on VTA dopamine neurons modulates food intake, perhaps by altering the motivation to consume or the incentive value of certain foods.

Whereas Hommel et al. (2006) focused specifically on the role of VTA dopamine neurons in the regulation of feeding by leptin, Fulton et al. (2006) asked more general questions about the role of leptin in regulating the activity of the mesolimbic dopamine pathway and its relationship to non-feeding-related motivated behaviors. Using double-label immunohistochemistry, they observed increased STAT3 phosphorylation in the VTA following peripheral leptin administration. These pSTAT3-positive neurons colocalized with TH and to a lesser extent with markers for GABA neurons. Retrograde neuronal tracing from the NAc revealed colocalization of tracer with pSTAT3, indicating that a subset of VTA dopamine neurons expressing leptin receptors project to the NAc.

In order to determine the effect of leptin on non-feeding-related motivated behaviors, Fulton et al. (2006) used wild-type (WT) and leptin-deficient *ob*/*ob* mice with or without chronic peripheral leptin replacement to assess changes in locomotor activity following repeated administration of amphetamine (AMPH). AMPH is well known to cause an increase in locomotor activity, and this effect gets significantly larger with subsequent administrations (i.e., sensitization). This phenomenon is mediated by activation of mesolimbic dopamine neurons (Vezina, 2004). In general, leptin increased the locomotor response to high-dose AMPH in WT and *ob*/*ob* mice. However, *ob*/*ob* mice failed to display locomotor sensitization to low-dose AMPH, and this defect was completely restored with chronic leptin replacement, implying that leptin signaling on mesolimbic dopamine neurons is required for behavioral sensitization.

Fulton et al. (2006) followed up these results by asking how leptin affects activity of the mesolimbic dopamine pathway. They found that, in the VTA, 3 day peripheral leptin treatment increased TH protein concentrations in *ob*/*ob* mice. In the NAc, they observed slightly different results in that leptin restored the reduced TH protein levels seen in *ob*/*ob* mice to control levels, and it increased phosphorylation of TH in *ob*/*ob* mice relative to vehicle and leptin-treated WT mice. Using in vivo electrophysiological recording from the NAc, Fulton et al. (2006) additionally found that *ob*/*ob* mice displayed decreased evoked dopamine release in the absence of changes in dopamine reuptake. Furthermore, they observed that NAc dopamine levels were lower in *ob*/*ob* mice versus WT mice.

The electrophysiological results of Fulton et al. (2006) are different from those of Hommel et al. (2006). A possible explanation for this discrepancy might be found in the models and paradigms used in these two studies. In fact, while Hommel et al. (2006) have observed the acute effect of leptin on the firing of dopamine neurons, Fulton et al. (2006) have used a genetic model characterized by leptin deficiency and obesity. In obese subjects, decreased dopaminergic activity and reduction of striatal D2 receptors have been interpreted as the cause for compensatory behaviors, such as overeating, that restore dopamine levels (Wang et al., 2001). However, a competing hypothesis suggests that the decrease in D2 receptors might be caused by increased activity of the dopamine pathway (Davis et al., 2004). Thus, the

findings from Fulton et al. (2006) might be the result of the obese phenotype on the activity of the dopaminergic pathway.

Taken together, the data from Hommel et al. (2006) and Fulton et al. (2006) indicate that leptin modulates the activity of mesolimbic dopamine neurons and that, in doing so, leptin may influence both food and drug-related behaviors. However, further investigation is needed to clarify the role of leptin in motivated behaviors other than feeding. For example, a clear link has been found between leptin and the endocannabinoids as reciprocal modulators of hypothalamic circuits underlying motivational aspects of feeding (Jo et al., 2005). Moreover, endocannabinoids positively regulate the mesolimbic dopamine pathway (Cota et al., 2006). Therefore, one hypothesis about the current findings is that leptin may act via changing levels of endocannabinoids to regulate dopamine neurons in the VTA and/or NAc. Future work will need to delineate just how the endocannabinoid system and leptin may interact in these brain areas.

The last decade has seen a vast increase in our understanding of the homeostatic regulators of feeding behavior; however, our ability to translate that into progress on how reward can influence both food intake and body weight has been considerably slower. The current work reflects how these two areas of study with quite different scientific histories are now coming together. The DiLeone group (Hommel et al., 2006) has worked primarily on various aspects of drug taking, but in this study they chose to investigate food intake as the primary endpoint. In contrast, the Flier group (Fulton et al., 2006) has worked primarily on the homeostatic aspects of food intake regulation, but here they chose to study the ability of leptin to alter the effects of a drug of abuse. This illustrates that investigators on both sides of this divide are coming to the conclusion that there are common underlying neuronal processes involved in drug abuse and obesity. Progress on these circuits has the promise to help develop treatment strategies to lower the enormous burden of both of these diseases.

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Multiple Memory Mechanisms in the Cerebellum?

Long-term potentiation (LTP) and long-term depression (LTD) are arguably two of the most widely discussed cellular plasticity mechanisms for learning and memory. However, the extent to which they are required for behavioral plasticity and learning is not clear. In this issue of *Neuron*, Boyden et al. use mice lacking CaMKIV and Hansel et al. use mice lacking αCaMKII to assess the contribution of LTD to cerebellar learning.

The two most widely studied and best understood forms of cerebellar-dependent learning and memory are adaptation of the vestibule-ocular reflex (VOR) and classical conditioning of eyeblink and other discrete responses (Christian and Thompson, 2003; du Lac et al., 1995). The VOR acts to counterbalance the effect of head movement by producing compensatory eye movements in the opposite direction of head movement, which thereby stabilizes images on the retina and prevents blurred vision. Adaptation of the VOR and eyeblink conditioning have somewhat analogous structural bases. In both cases, adaptation in initial cerebellar learning critically involves the cerebellar cortex, while the cerebellar and vestibular nuclei play a more critical role in long-term memory storage (Christian and Thompson, 2005; du Lac et al., 1995; Kleim et al., 2002).

What are the cellular and molecular mechanisms that underlie cerebellar learning? In vitro studies have pointed to a large number of plasticity mechanisms operational within the cerebellar circuits. However, the contribution of these mechanisms to specific forms of behavioral plasticity remains less clear. Ito first proposed cerebellar LTD as the mechanism in the cerebellar flocculus for adaptation of the VOR (Ito, 1982). Cerebellar long-term depression (LTD) is also widely viewed as a possible mechanism of synaptic plasticity of other forms of cerebellar-dependent learning as well (Linden and Connor,